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b. Prevent and Cure Disuse Bone Loss

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II. OBJECTIVES AND HYPOTHESES

1) Disuse-related osteopenia and poor trabecular architecture is prevented by non-steroidal anti-inflammatory drugs (NSAID).

2) Established disuse-related osteopenia and poor trabecular architecture is cured by PGE_2 or PTH treatment though immobilization continues.

3) Though bone mass returns, poor trabecular architecture remains after normal ambulation recovery from immobilization.

4) Established disuse-related bone loss and poor trabecular architecture is cured by post-immobilization PGE_2 treatment.

III. SUMMARY OF FINDINGS

1. PGE_2 Treatment Prevented Immobilization-induced Bone Loss.

   A. PGE_2 administration not only prevented immobilization-induced bone loss, but also added extra bone in a dose-response manner. It stimulated more bone formation than resorption shortened the period of bone remodeling, activated woven bone formation, stimulated lamellar bone formation and shortened the bone resorption and remodeling period to reduce the remodeling space (T. Akamine et al., Prostaglandin E_2 prevents bone loss and adds extra bone to immobilized distal femoral metaphysis in female rats. Bone 13:11-22, 1992)

   B. PGE_2 treatment-induced increases in periosteal and endocortical bone formation to compensate for the disuse and PGE_2-induced cortical bone loss, and thus prevented immobilization-induced cortical bone loss (W.S.S. Jee et al. Prostaglandin E2 prevents disuse-induced cortical bone loss. Bone 13:153-159, 1992).

2. S-ketoprofen, a non-steroidal anti-inflammatory drug prevented immobilization-induced bone loss, but not changes in architecture.

   A. S-ketoprofen, a non-steroidal anti-inflammatory drug, prevented both the inhibition of age-related cancellous bone gain and the stimulation of bone loss induced by immobilization (tenotomy) at the 2.5 mg/kg/d, while it only prevented bone loss at the 0.5 mg/kg/d dose levels. These doses partially protected from the development of poor architecture in that trabecular numbers were reduced.

   B. In the tibial shaft, S-ketoprofen prevented the immobilization-induced increase in endocortical bone resorption (Q.Q. Zeng et al. S.-Ketoprofen inhibits tenotomy-induced bone loss and dynamics in weanling rats. Bone and Mineral 21:204-218, 1993).

3. PGE_2 restored bone and structure to immobilization-induced osteopenic rats.
Daily 3 or 6 mg/kg/d treatment restores and maintains proximal tibial metaphyseal cancellous bone mass and structure in continuously immobilized tibiae in female rats in spite of continuous immobilization (M. Li et al. Prostaglandin E_2 restores cancellous bone to immobilized limb and adds bone to overloaded limb in right hindlimb immobilization rats. Bone 14:283-288, 1993).

4. Parathyroid hormone (PTH) restores and adds extra cancellous bone and improves bone structure to immobilized, osteopenic proximal tibial metaphysis in rats.
PTH treatment stimulates cancellous bone formation, restores and adds extra cancellous bone and improves bone structure above that of age-related controls in established, disuse-osteopenic proximal tibial metaphysis of continuously right hindlimb immobilized female rats (Y.F. Ma et al. Human parathyroid hormone (1-38) restores cancellous bone to the immobilized, osteopenic tibial metaphysis in rats. J. Bone and Mineral Research (in press)).

5. Remobilization after short term immobilization (2 weeks) allows normal bone mass and architecture to return while longer immobilization (> 10 weeks) does not in rats.
(X.G. Liang et al. Effects of remobilization on the immobilization-induced osteopenic rat skeleton. A time response study. In preparation)

IV. CONTRIBUTIONS TO A BETTER UNDERSTANDING OF BONE BIOLOGY.

1. We found that a powerful anabolic agent like PGE_2 will stimulate direct bone formation during bone modeling and remodeling (1-18).
2. We found that PGE_2 shortens the phases of the bone remodeling cycle. It reduces the residence time of the remodeling space and enables the agent to activate new bone turnover sites with a smaller transient bone loss phase that could place an individual at increased fracture risk (1-18)
3. We confirm that bone tissue precedes bone marrow in ontogeny (11,19,20).
4. Our studies confirm that cortical bone contains a rich source of osteoblastic progenitors, believed to be the lining cells of the cortical bone vascular channels (2,3,4,8,11,13,15).
5. We found bone mass increases caused by anabolic agents do not continue indefinitely. One might suggest that they plateau at a new level commensurating with the properties of the agent, dose, and the role of skeletal adaptation to mechanical usage (4,6).

6. Our studies indicate that excess bone induced by an anabolic agent disappears after treatment stops. We postulate that bone adapts to mechanical usage by ridding itself of "extra" bone that keeps strain "too low" or adding "extra" bone when strain is "too high" to maintain constant strain within the physiologic window (9,11,17,191,20).
7. In our studies we discovered that we could outsmart the skeleton by using the lose, restore and maintain (LRM) concept to restore and maintain PGE_2 added cancellous and supplement and maintain (SM) concept to build up bone (11,17).
8. We found PGE_2 will stimulate periosteal bone formation and consequently increase the diameter of the cortex and its strength. The engineers tell us that the strength of a given mass can be increased by increasing the diameters of the shaft while making its wall proportionally thinner (2-4,8,13).
9. We found that PGE_2 depresses longitudinal bone growth in male but stimulates it in female immobilized rats. This is an area of research that warrants more study (21).
10. We confirm that the distal tibial metaphysis (DTM) closes at 3 months and a few months later contains a metaphysis with fewer but thicker trabeculae and lower turnover. Studies of this adult metaphysis could improve our under standing of the responses of this adult cancellous bone as well as a low turnover site to bone-seeking agents inexpensively (14,15,18).
11. We discovered that ovariectomize does <u>not</u> but immobilization does induce bone loss in the adult distal tibial metaphyses (18,22).

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V. CONCLUDING REMARKS.

If remobilization after long-term immobilization is incapable of restoring normal bone mass and structure in humans as seen in rats and dogs, anabolic agents like parathyroid hormone and prostaglandin E-like substances will be needed. It is fortunate that several pharmaceutical companies are developing analogues of these two agents. If successful, these agents will be effective for all types of osteoporoses in man if they are tested in an immobilization-induced bone loss model because immobilization-induced bone loss is more difficult to prevent and cure than estrogen-deficiency-induced osteopenia.

REPRINTS

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1. Jee, WSS, Ke, HZ, Li, XJ. 1991 Long-term anabolic effects of prostaglandin-E_2 on tibial diaphyseal bone in male rats. Bone and Mineral 15:33-55.
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